Wednesday, March 6, 1991
2:00PM–3:30PM, Room 254, West Concourse
Clinical Pharmacology: Central Nervous System Mechanisms

2:00

DOBUTAMINE IS A PARTIAL AGONIST WITH AN INTRINSIC ACTIVITY OF 0.5 IN HUMAN MYOCARDIUM.

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Previous animal studies have demonstrated that dobutamine (DBT), a mildly (3-4 fold) selective $ß_1$ agonist, has an intrinsic activity (relative to isoproterenol (ISO)) of .8 to 1.0. Because of species variation in ß adrenergic receptor-effector mechanisms we assessed the activity of DBT in human myocardial ß adrenergic receptor systems. We examined the contractile response of DBT and ISO in isolated right ventricular trabeculae prepared from end stage failing hearts (n=16) removed from transplant recipients and nonfailing hearts (n=6) taken from organ donors. Additionally, ß adrenergic receptor density, $ß_1/ß_2$ receptor subtype distributions and adenylate cyclase (AC) activity were measured in crude myocardial membranes: (values ± SEM)

	NET TENSION (mg)		A.C. (pmol cAMP/min/mg)		RECEPTORS (fmol/mg)		
	ISO	DBT	ISO	DBT	ß Total	$ß_1$	$ß_2$
NF	2262	#1158	43.1	#15.4	83.3	64.8	18.8
	±83	±385	±1.7	±5.2	±8.1	±6.3	±1.8
F	*1211	*425	25.6	3.5	*56.9	*32.7	23.7
	±173	±73			±4.4	±2.5	±1.8

*,p <.05 vs NF; #,p <.05 vs ISO

The tension data yield an intrinsic activity for DBT of .51 in nonfailing and .44 in failing myocardium.

CONCLUSION: DBT has relatively less efficacy in human compared to animal myocardium, perhaps because of a lower coupling ratio and no receptor reserve in the human heart. The partial agonist properties of DBT must be kept in mind in clinical situations that call for maximal inotropic stimulation.

2:15

EFFECT OF LONG TERM THROMBOXANE A2 RECEPTOR BLOCKADE ON ANGIOGRAPHIC RESTENOSIS AND CLINICAL EVENTS AFTER CORONARY ANGIOPLASTY. THE CARPORT STUDY.

P.W. Serruys, W. Rutsch, G. Heyndrickx, N. Danchin, G. Mast, W. Wijns, B.J. Rensing, for the Carport study group

GR32191B is a novel thromboxane A2 receptor antagonist with potent antiaggregational and anti-vasoconstrictive properties. To study whether this compound is useful in restenosis prevention after coronary angioplasty (PTCA), we have conducted a randomised, double blind, placebo controlled trial. Patients (pts) were randomized to receive either GR32191B, 80 mg intravenous before PTCA and 40 mg orally for 6 months, or 250 mg intravenous aspirin before PTCA and placebo for 6 months. Coronary angiograms before PTCA, after PTCA and at 6 months follow up were quantitatively analyzed, using an automated edge detection technique.

PTCA was attempted in 697 pts. Failure of the procedure occurred in 47 pts (6.7%). Follow up angiography was available in 88.5% (575 pts) of successfully treated pts. In 53 pts drug compliance was less then 80% or trial medication was discontinued for more then 3 consecutive days. Quantitative data from these pts were excluded from analysis in accordance with the protocol. Baseline clinical and angiographic parameters did not differ between the two treatment groups. Multiple matched view analysis was performed on 306 segments (281 pts) in the placebo group (plgr) and on 308 segments (261 pts) in the active treatment group (trgr).

The mean coronary diameter (cordia) after PTCA was 1.77 ± 0.35 mm in the plgr and 1.79 ± 0.33 mm in the trgr (NS). Cordia at follow up angiography was 1.46 ± 0.59 mm in the plfgr and 1.49 ± 0.58 mm in the trgr. The mean difference in coronary diameter between post PTCA and follow up angiogram, as a measure for intimal hyperplasia, was -0.31 ± 0.53 mm in the plgr and -0.30 ± 0.54 mm in the trgr (NS).

Clinical events during follow up, analyzed on intention to treat basis, are ranked according to the highest category on a scale ranging from death (plgr 3, trgr 2), nonfatal infarction (plgr 20, trgr 15), bypass grafting (plgr 16, trgr 23), re-PTCA (plgr 52, trgr 47), NYHA class III/IV (plgr 33, trgr 35), NYHA class II (plgr 70, trgr 76) to no event (plgr 132, trgr 133). No significant difference in ranking was detected between the two treatment groups.

Long term thromboxane A2 receptor blockade with GR32191B, used as a single pharmacologic regimen, does not prevent intimal hyperplasia and does not favourably influence the longterm clinical course following PTCA.

2:30

THE EFFECT OF ATENOLOL AND DILTIAZEM ON PARASYMPATHETIC NERVOUS ACTIVITY IN NORMAL SUBJECTS

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After myocardial infarction (MI), low parasympathetic activity (PSA) is associated with high rates of mortality and malignant ventricular arrhythmias. Beta blockers (ßB) and calcium channel blockers (CCB) are commonly used after MI, but the effects of these drugs on PSA is unknown. To determine the effect of ßB and CCB on PSA, we treated 16 normal subjects, aged 32±7 (range 25 - 55) years, with atenolol (50 mg QID), diltiazem (60 mg QID), and placebo (QID) in a double-blind, randomized, cross-over study design. Subjects had a 24-hour ECG recording done on each treatment. QRS complexes were labeled on a Marquette scanner and heart period variability calculations were done on a Sun 3/160 computer. The doses of atenolol used blocked the increase in low frequency power seen during 60° head up tilt on placebo treatment, indicating excellent ß-adrenergic blockade. 24-Hour average PSA was measured with: the proportion of successive normal RR (NN) interval differences >50 msec (pNN50), the root mean square successive difference of NN (r-MSSD), and the high frequency (HF) power band (0.15 - 0.40 Hz) of the heart period power spectrum. Treatment effects were as follows.

	Atenolol	Diltiazem	Placebo
Average NN	1039±112*	847±90	836±88
r-MSSD	87±29*	61±27	54±22
pNN50	44±12*	28±14	26±12
HF Power	2104±1216*	1510±1402	1146±1070

* differs from placebo at p <0.001

Conclusions:

On placebo, PSA was much greater in normal subjects than in patients after myocardial infarction. ßB caused a large increase in PSA, an effect which stabilizes the heart electrically. CCB had no effect on PSA. The differences between ßB and CCB effects on PSA may explain, in part, the improved survival after MI associated with ßB, but not with CCB, treatment.

2:45

USE OF LOW DOSE INTRAVENOUS BOLUS ADENOSINE FOR DETERMINATION OF CORONARY VASODILATORY RESERVE IN PATIENTS

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Continuous intravenous infusion of adenosine produces coronary hyperemia equivalent to intracoronary papaverine (PAP) and is useful for extended coronary hyperemic stimulation without adverse electrophysiologic effects. To assess whether low dose single IV bolus adenosine produces comparable coronary hyperemia, we measured coronary blood flow velocity (20Mhz Doppler catheter), heart rate and mean arterial pressure in 17 pts (7 with and 10 without coronary artery disease) at rest and during maximal hyperemia during 10mg intracoronary PAP, 3 minute IV infusion 100mcg/kg adenosine (AD100) and during IV bolus 2.5mg adenosine (AD2.5). Coronary reserve (CVR) was calculated as peak hyperemic/basal mean velocity (MV). Results: (mean+SD) (*p<0.05 vs PAP)

	AD100	PAP	AD2.5
CVR (units)	2.27±0.73	2.47±1.35	2.17±0.91*
MV (cm/sec)	60±30	68±30	58±23*

Correlation between methods (AD100 vs PAP, AD100 vs AD2.5 and PAP vs AD2.5) for CVR were r=0.830, 0.725 and 0.914 and for MV, r=0.872, 0.765 and 0.844, respectively (all p<0.001). Time to peak hyperemia from femoral vein injection was 17±6 seconds with return to baseline by 20±5 seconds. An additional IV bolus 5mg adenosine failed to augment the mean velocity achieved with 2.5mg in 7/9 pts. These data indicate that low dose IV bolus adenosine produces transient coronary hyperemia equivalent to prolonged IV infusion, but lower than intracoronary PAP, and is suitable for repetitive determinations of CVR in pts.